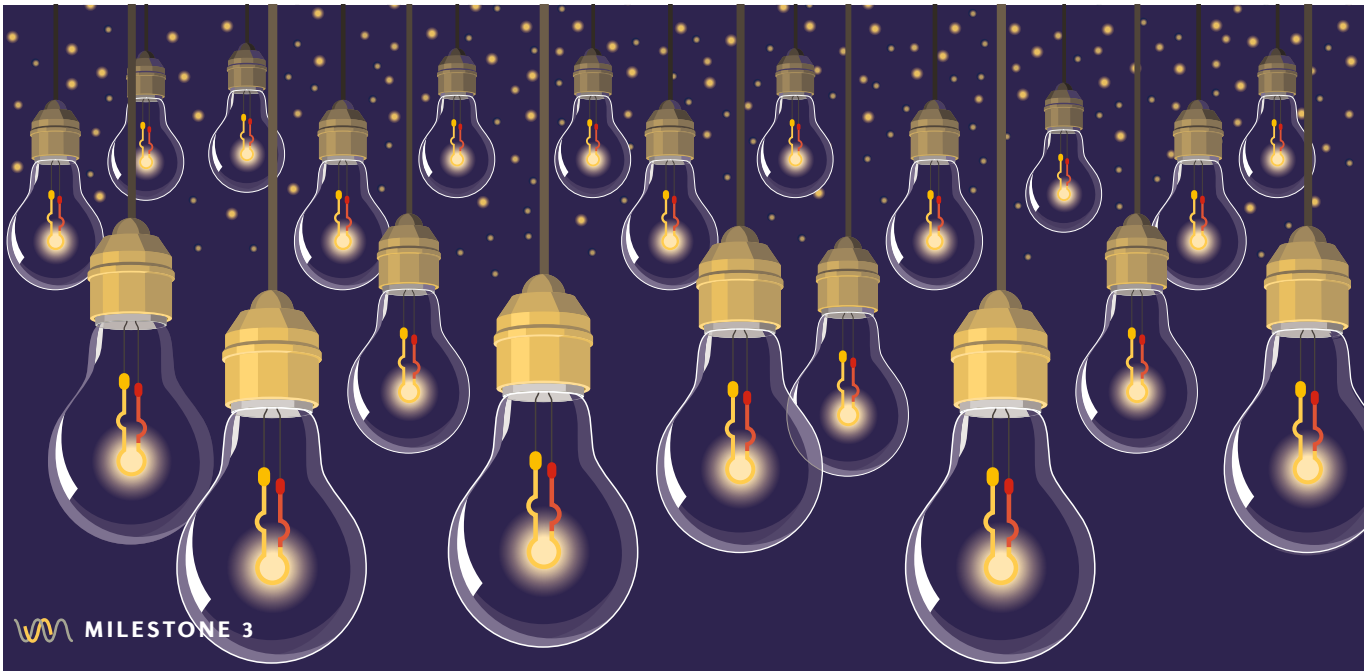

MILESTONE 3

microRNAs emerge as potent post-transcriptional gene regulators

There is nothing more precise than a Swiss watch — besides the pattern of development of the nematode worm *Caenorhabditis elegans*, one of the most studied and useful animal models. The postembryonic development of *C. elegans* entails passage through four accurately coordinated larval stages (L1–L4) interspersed with moults. In the mid-1980s, many scientists were interested in genetic aberrations that could alter the precise timing of *C. elegans* development. Genes that, when manipulated, could delay or advance the nematode's cell cycle and developmental-stage progression were called heterochronic genes. As expected at the time, most of these genes encode proteins.

In 1993, Victor Ambros and colleagues demonstrated that down-regulation of the protein LIN-14 was crucial for the progression from the first larval stage (L1) to the second larval stage (L2). Loss-of-function mutations in *lin-14* cause *C. elegans* to skip a beat, starting development from L2. On the other hand, mutations in another gene, *lin-4*, halted developmental progression indefinitely at the L1 stage. Surprisingly, *lin-4* did not encode a protein; instead, it is transcribed into a small non-coding RNA with sequence complementarity to the 3′ untranslated region (3′ UTR) of *lin-14*. Lin-4 was the first microRNA to be discovered.

At the same time, Gary Ruvkun and colleagues showed that binding of lin-4 to the 3′ UTR is essential for LIN-14 downregulation. Both teams correctly hypothesised that lin-4 pairs through antisense complementarity to the 3′ UTR of *lin-14*, and forms an RNA duplex that leads to translational repression of *lin-14*. Although lin-4 binding did not affect the overall mRNA levels of *lin-14*, it decreased LIN-14 protein expression, subsequently causing progression from L1 to L2.

This novel mechanism of post-transcriptionally regulating gene expression was shown, in both articles, to be conserved in several worm species, but at the time it was mostly thought to be a nematode oddity. During the 1990s, a second microRNA regulating *C. elegans* development was identified and named let-7. In the case of let-7 mutant nematodes, larvae stopped just short of becoming adult worms. Lin-4 and let-7 were quite different from each other but, in 2000, Ruvkun and colleagues found homologues in the genomes of *Drosophila melanogaster* and *Homo sapiens*. Although humans have no heterochronic genes, fruit flies do, and the temporal expression profile of let-7 was shown to be conserved between worms and fruit flies.

> “… although lin-4 binding did not affect the overall mRNA levels of *lin-14*, it decreased LIN-14 protein expression…”

Since the discovery of lin-4 and let-7, many microRNAs have been identified. This family of small non-coding RNAs is involved in the regulation of diverse biological processes, and includes many potential therapeutic targets — not bad for what were originally thought to be mere worm time-keepers.

Anne Mirabella,
Senior Editor, *Nature Communications*

MILESTONE STUDIES Lee, R. C. et al. The *C. elegans* heterochronic gene *lin-4* encodes small RNAs with antisense complementarity to *lin-14*. *Cell* **75**, 843–854 (1993) | Wightman, B. et al. Posttranscriptional regulation of the heterochronic gene *lin-14* by *lin-4* mediates temporal pattern formation in *C. elegans*. *Cell* **75**, 855–862 (1993).
FURTHER READING Pasquinelli, A. E. et al. Conservation of the sequence and temporal expression of *let-7* heterochronic regulatory RNA. *Nature* **408**, 86–89 (2000).